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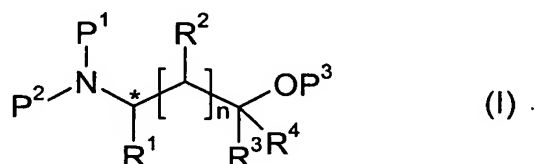
Process for the hydrogenation of aromatic compounds

Cross Reference to Related Applications

The present application represents U.S. national stage of international application PCT/EP2004/006654, which has an international filing date of June 19, 2004, and which was published in English under PCT Article 21(2) on February 17, 2005. The international application claims priority to German application 103 33 588.9, filed on July 24, 2003. These prior applications are hereby incorporated by reference in their entirety.

Field of the Invention

The present invention concerns a process for the hydrogenation of aromatic or heteroaromatic compounds. In particular, the invention concerns the hydrogenation of aromatic compounds such as (I)



in the presence of a platinum-rhodium mixed catalyst.

Background of the Invention

The hydrogenation of aromatic compounds is a standard reaction in organic chemistry and the resulting products are utilised commercially in many products.

Ring-hydrogenated amino acids and derivatives thereof, as structural mimetics of the natural amino acids valine and isoleucine, are interesting building blocks in peptide chemistry, for example (J. Med. Chem. **1993**, 36, 166; Coll. Czech. Chem. Commun. **1984**, 49, 712; Coll. Czech. Chem. Commun. **1966**, 31, 4563; Synthetic Communications, **1978**, 8, 345), and are used in a number of active ingredients, particularly renin inhibitors (e.g. WO 91/07430, EP 438311

and EP 427939) and thrombin inhibitors (e.g. melagatran and ximelagatran, Drugs of the Future 2001, 26, 1155). There is therefore a corresponding level of interest in the economical production of such amino acids on an industrial scale.

One possibility for the production of these compounds is the hydrogenation of corresponding aromatic precursors, many of which are available at a reasonable cost in enantiopure form (e.g. phenylalanine, phenylglycine and tyrosine). However, although the hydrogenation of simple, unsubstituted aromatic hydrocarbons to the corresponding saturated compounds under pressure in the presence of a noble metal catalyst is relatively straightforward, the hydrogenation of substituted aromatics is substantially more difficult. Secondary reactions can occur, such as e.g. a hydrogenolytic cleaving of substituents, particularly if palladium and platinum catalysts are used (Synthetic Communications, 1999, 29, 4327). Detailed investigations of the reactions are therefore necessary in many of these cases in order to optimise the reaction conditions (J. Org. Chem., 1958, 23, 276; Org. Syn., 1947, 27, 21).

An additional problem occurs if the substituent is carrying an asymmetrical C atom (particularly if it is in the benzyl position), since there is always a danger of partial racemisation (Synthetic Communications, 1978, 8, 345; EP 0823416). The racemisation-free hydrogenation of e.g. phenylglycine to cyclohexylglycine is therefore an especially critical reaction.

Several processes for the hydrogenation of phenylglycine, phenylalanine and other amino acids having aromatic substituents are described in the literature. Palladium, PtO₂ (Adam's catalyst), platinum, ruthenium and rhodium were used therein as catalysts.

However, as a consequence of the hydrogenolytic cleaving of the benzyl amino group that occurs as a secondary

reaction, the hydrogenation of phenylglycine with $\text{Pd}(\text{OH})_2$ (Synthetic Communications, **1978**, 8, 345) generates only moderate yields. In addition, the cyclohexylglycine produced in this way was partially racemised.

5 The use of PtO_2 as a hydrogenating catalyst is described in a large number of publications. However, in most cases (US 4788322; J. Org. Chem., **1988**, 53, 873; TH **1992**, 48, 307; THL **1996**, 37, 1961; TH **1998**, 54, 5545) only phenylalanine was hydrogenated, so no conclusion can be
10 drawn about racemisation in the benzyl position. In two cases phenylglycine is also described as an educt (J. Am. Chem. Soc., **1982**, 104, 363; Chem. Berichte **1986**, 119, 2191). In the second case at least, a partial racemisation of the product is probable because of the specified angle
15 of rotation. Other disadvantages of this method are the relatively long hydrogenation times (18 h) and the use of acetic acid as solvent, since this makes it more difficult to isolate the products.

Platinum itself has also been used as a catalyst (J. Chem. Soc. C, **1968**, 531; THL, **1991**, 32, 3623), although only the
20 hydrogenation of phenylalanine is described in these cases, so again no conclusion can be drawn about a possible racemisation. In addition, no details are given of yields or of the pressures, reaction temperature and
25 reaction times required. On the basis of the details given in Synthetic Communications, **1999**, 29, 4332, however, it must be assumed that these hydrogenation reactions do not proceed particularly advantageously.

Patent EP 0823416 describes the use of a ruthenium
30 catalyst for the hydrogenation of phenylglycine and phenylalanine, although at 65% the yields are moderate and unacceptable on an industrial scale.

Finally, rhodium catalysts have also been used for the hydrogenation of phenylglycine (Synthetic Communications,
35 **1999**, 29, 4327). In this case, however, the hydrogenation times (40 h) are very long, despite the use of more than

10 wt.% catalyst. Furthermore, a major disadvantage of the pure rhodium catalyst described here (5% Rh/C) is the high price of rhodium, which is by far the most expensive of the noble metals mentioned here.

5 Description of the Invention

The object of the present invention was therefore to provide details of another process for the hydrogenation of aromatic radicals of compounds having formula (I), which helps to prevent the aforementioned disadvantages of
10 the prior art processes, particularly with regard to yield and risk of racemisation. This process should moreover also be able to be used on an industrial scale, i.e. it should be particularly advantageous from both an economic and an ecological perspective.

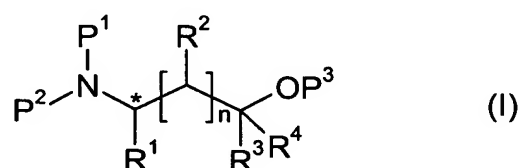
15 These and other objects not specified in any more detail, but obviously deriving from the prior art, are achieved by a process having the characterising part of claim 1. Claim 2 is limited to the hydrogenation of certain aromatic compounds. The dependent claims 3 to 9 relate to
20 preferred embodiments of the process according to the invention.

Quite surprisingly, but no less advantageously for that, the stated objects are achieved particularly simply according to the invention in that in a process for the
25 hydrogenation of aliphatic-substituted aromatic or heteroaromatic compounds having an asymmetrical C atom, hydrogenation is performed in the presence of a platinum-rhodium mixed catalyst. When used according to the invention the proposed catalyst material leads to an
30 almost completely racemisation-free hydrogenation product. With figures in some cases well above 94%, the yields are at the upper end of what is technically feasible. This shows that the formation of secondary products is inhibited correspondingly. A further advantage can be seen
35 in the fact that the actual hydrogenation is completed in extremely short times of around 6 to 8 hours, which

advantageously helps to raise the space-time yield, which is especially critical on an industrial scale.

Aromatic or heteroaromatic compounds displaying the asymmetrical site in the benzyl position are preferred.

- 5 In a second aspect the invention relates in particular to a process for the hydrogenation of the aromatic nucleus of compounds having the general formula (I)



wherein

- 10 n can be 0, 1, 2

R¹ represents unsubstituted or substituted (C₆-C₁₈) aryl, (C₇-C₁₉) aralkyl, ((C₁-C₈) alkyl)₁₋₃ (C₆-C₁₈) aralkyl ((C₁-C₈) alkyl)₁₋₃ (C₆-C₁₈) aryl, (C₃-C₁₈) heteroaryl, (C₄-C₁₉) heteroaralkyl, ((C₁-C₈) alkyl)₁₋₃ (C₃-C₁₈) heteroaryl,

- 15 R² denotes H, OH, (C₁-C₈) alkyl, (C₂-C₈) alkoxyalkyl, (C₆-C₁₈) aryl, (C₇-C₁₉) aralkyl, (C₃-C₁₈) heteroaryl, (C₄-C₁₉) heteroaralkyl, ((C₁-C₈) alkyl)₁₋₃ (C₆-C₁₈) aryl, ((C₁-C₈) alkyl)₁₋₃ (C₃-C₁₈) heteroaryl, (C₃-C₈) cycloalkyl, ((C₁-C₈) alkyl)₁₋₃ (C₃-C₈) cycloalkyl, (C₃-C₈) cycloalkyl (C₁-C₈)

- 20 alkyl,

R³ and R⁴ together denote an =O function or H, (C₁-C₈) alkyl, (C₆-C₁₈) aryl,

P¹ and P² mutually independently stand for hydrogen or an amino protective group or together stand for a

- 25 bifunctional amino protective group,

P³ represents hydrogen or a hydroxyl protective group or carboxyl protective group and

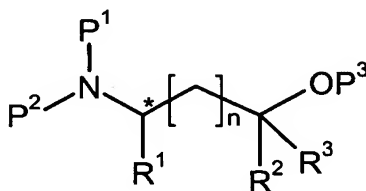
the C atom marked with * is an asymmetrical C atom, this hydrogenation being performed in the presence of a

- 30 platinum-rhodium mixed catalyst. In the hydrogenation

according to the invention the same advantages are found for the compounds claimed here as are described above. All natural and synthetic aromatic amino acids familiar to the person skilled in the art can be used according to the invention as educt, in particular α - and β -amino acids or the amino alcohols produced therefrom by reduction of the carboxyl function. Examples of natural amino acids can be found in Bayer-Walter Lehrbuch der organischen Chemie, 1991, S. Hirzel Verlag, 22nd edition, p. 822ff. Preferred synthetic amino acids are cited in DE19903268.

The amino acids can be used in the reaction in protected or unprotected form. Protective groups that are inert in respect of hydrogenation are preferred. A list of common amino acid protective groups is given in Green et al. (Greene, T.W., Protective Groups in Organic Synthesis, J. Wiley & Sons, 1981). Examples of amino protective groups that are preferably used are: acetyl, MoC, EOC, formyl, tert-butyl oxycarbonyl. Examples of carboxyl protective groups and hydroxyl protective groups can likewise be found in Green et al. They are in particular esters such as e.g. benzyl, tert-butyl, ethyl and methyl ester. In terms of the hydroxyl protective group, ethers such as tert-butyl, methyl, methoxymethyl or acyl protective groups such as formyl or acetyl are suitable. The protected derivatives of the aromatic amino acids can be produced from the free amino acids by simple means using standard methods (Houben-Weyl Volume XV/1, 1974, Georg Thieme Verlag).

Compounds having the general formula II



(II)

wherein

n is 0,1,

R¹ represents unsubstituted or substituted (C₆-C₁₈) aryl, (C₇-C₁₉) aralkyl, ((C₁-C₈) alkyl)₁₋₃ (C₆-C₁₈) aryl radicals,

5 R² and R³ are H or together are =O,

P¹ and P² mutually independently stand for hydrogen or an amino protective group or together stand for a bifunctional amino protective group,

10 P³ represents hydrogen, a hydroxyl protective group or a carboxyl protective group and

the C atom marked with * is an asymmetrical C atom, are preferably used in the reaction according to the invention. Examples thereof are L-phenylalanine, D-phenylalanine, L-phenylglycine, D-phenylglycine, L-tyrosine and D-tyrosine.

In principle the person skilled in the art is free to choose the relative composition of the hydrogenating catalyst. He or she will be guided here by operational results and by the costs of materials. The optimum
20 composition can then be determined by routine experiments. A process in which a ratio of platinum to rhodium of between 20:1 and 1:1 (w/w) is used in the catalyst is preferred. The ratio is most particularly preferably 10:1 to 2:1, extremely preferably 5:1 to 3:1 (w/w).

25 The amount of catalyst to be used can be chosen freely by the person skilled in the art. In this case too, the aim should be to optimise the reaction in terms of economic perspectives. The catalyst is preferably used in a quantity of 0.1 to 20 wt.%, relative to the compound to be
30 hydrogenated. The quantity is most preferably 1 to 15 wt.%, extremely preferably between 2 and 10 wt.%.

The catalyst is advantageously used in the supported state. This means that the catalyst is adsorbed on a support. All compounds used by the person skilled in the
35 art for this purpose can serve as support materials. A list of suitable materials can be found in Ullmann's

Encyclopedia of Industrial Chemistry, Volume A5, VCH, 1986, p. 347ff and in literature cited therein, and in Houben-Weyl, Methoden der Organischen Chemie, Volume 4/2, p. 146 ff. Of these, activated carbon and aluminium oxide
5 should be emphasised in particular.

The platinum-rhodium catalysts that are used can contain between 1 and 10 wt.% noble metal (relative to the support), 4 to 6 wt.% being particularly preferred.

The hydrogenation according to the invention can be
10 performed in solvents used for this purpose by the person skilled in the art. These are in particular those that are inert in respect of hydrogenation and that dissolve both educts and products to an adequate extent. The hydrogenation is preferably performed in the presence of
15 solvents selected from the group comprising water, alcohols, ethers or mixtures thereof. In the hydrogenation of unprotected or only amino-protected or only hydroxyl/carboxyl-protected aromatic amino acids, it can be advantageous to add at least 1 equivalent of a base (for
20 unprotected or only N-protected amino acids) or 1 equivalent of an acid (for unprotected or only hydroxyl/carboxyl-protected amino acids). Examples of bases that can be used here are NaOH, KOH, NH₃ or amine bases such as triethylamine. Examples of acids are HCl, H₂SO₄, H₃PO₄,
25 acetic acid and trifluoroacetic acid.

The hydrogen pressure that should be present during the reaction can be freely chosen by the person skilled in the art, depending on the speed of hydrogenation or possibly on the presence in the substrate to be hydrogenated of
30 functional groups that are vulnerable to hydrogenation. The hydrogenation is preferably performed under hydrogen pressures of between 1 and 100 bar. Also preferred are pressures of between 5 and 15 bar, to ensure a correspondingly rapid hydrogenation.

35 The temperatures during hydrogenation should be in the range that appears normal to the person skilled in the

art. A temperature of 10°C to 150°C is preferred. The process is most particularly preferably performed at between 30°C and 80°C.

If enantiomer-concentrated substrates are used in the present process, the hydrogenation is very stereoconservative. The degree of racemisation is generally <10%, preferably <5%, more preferably <4% and most particularly preferably <3%. In an extremely preferred embodiment, the racemisation during the reaction can be <2% and even <1% and below.

The process provided by the invention is preferably performed in such a way that the compound to be hydrogenated is dissolved in the appropriate solvent, the catalyst is added and in a suitable apparatus the gas chamber, which has first been rendered inert, is supplied with hydrogen under a certain pressure. The stirred suspension is generally fully hydrogenated in 6 to 8 hours. The yields are close to 100% and the degree of racemisation, even with vulnerable substrates (phenylglycine) is less than 0.5%. It is precisely the combination of the possibility of being able to use expensive rhodium in tiny amounts, combined with the unexpectedly fast hydrogenation with optimum yields and enantiomer concentrations in the product, that puts these hydrogenation catalysts for the reaction according to the invention, which clearly stands out inventively from the prior art processes, in an exceptional position. Furthermore, the catalysts that are used can be recycled very effectively and reused in the reaction with no loss of activity. This also helps to save on operating costs, since on average less catalyst has to be used per quantity of substrate.

(C₁-C₈) alkyl radicals should be understood to be methyl, ethyl, *n*-propyl, isopropyl, *n*-butyl, isobutyl, *sec*-butyl, *tert*-butyl, pentyl, hexyl, heptyl or octyl together with

al their bond isomers. These can be substituted with one or more halogen, OH, NH₂, NHR² or N(R²)₂ radicals.

The (C₁-C₈) alkoxy radical corresponds to the (C₁-C₈) alkyl radical, with the proviso that it is bonded to the
5 molecule by an oxygen atom.

Radicals in which the alkyl chain is interrupted by at least one oxygen function, wherein two oxygen atoms cannot be connected to one another, are intended as (C₂-C₈) alkoxyalkyl. The number of carbon atoms indicates the
10 total number of carbon atoms contained in the radical.

(C₃-C₈) cycloalkyl is understood to be cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl or cycloheptyl radicals, etc. These can be substituted with one or more halogens and/or radicals containing N, O, P, S, Si atoms
15 and/or display N, O, P, S atoms in the ring, such as e.g. 1-, 2-, 3-, 4-piperidyl, 1-, 2-, 3-pyrrolidinyl, 2-, 3-tetrahydrofuryl, 2-, 3-, 4-morpholinyl.

A (C₃-C₈) cycloalkyl (C₁-C₈) alkyl radical denotes a cycloalkyl radical as described above, which is bonded to
20 the molecule by an alkyl radical as specified above.

Within the meaning of the invention (C₁-C₈) acyloxy denotes an alkyl radical as defined above having a maximum of 8 C atoms, which is bonded to the molecule by a COO function.

Within the meaning of the invention (C₁-C₈) acyl denotes an
25 alkyl radical as defined above having a maximum of 8 C atoms, which is bonded to the molecule by a CO function.

A (C₆-C₁₈) aryl radical is understood to be an aromatic radical having 6 to 18 C atoms. Examples include in particular compounds such as phenyl, naphthyl, anthryl,
30 phenanthryl, biphenyl radicals or systems of the type described above which are annelated to the molecule concerned, such as e.g. indenyl systems, which can optionally be substituted with halogen, (C₁-C₈) alkoxy, (C₁-C₈) acyl, (C₁-C₈) acyloxy.

A (C₇-C₁₉) aralkyl radical is a (C₆-C₁₈) aryl radical bonded to the molecule by a (C₁-C₈) alkyl radical.

Within the meaning of the invention a (C₃-C₁₈) heteroaryl radical denotes a five-, six- or seven-membered aromatic ring system comprising 3 to 18 C atoms, which displays heteroatoms such as e.g. nitrogen, oxygen or sulfur in the ring. Such heteroaromatics are understood in particular to be radicals such as 1-, 2-, 3-furyl, such as 1-, 2-, 3-pyrrolyl, 1-, 2-, 3-thienyl, 2-, 3-, 4-pyridyl, 2-, 3-, 4-, 5-, 6-, 7-indolyl, 3-, 4-, 5-pyrazolyl, 2-, 4-, 5-imidazolyl, acridinyl, quinolinyl, phenanthridinyl, 2-, 4-, 5-, 6-pyrimidinyl.

A (C₄-C₁₉) heteroaralkyl is understood to be a heteroaromatic system corresponding to the (C₇-C₁₉) aralkyl radical.

Suitable halogens are fluorine, chlorine, bromine and iodine.

The meaning of the expression "aromatic" or "heteroaromatic" is as understood by the general person skilled in the art. Definitions can be found e.g. in Bayer-Walter Lehrbuch der organischen Chemie, 1991, S. Hirzel Verlag, 22nd edition, p. 469ff. and p. 656 or p. 704ff.

Within the meaning of the invention, the term enantiomer-concentrated or enantiomer excess is understood to be the content of an enantiomer mixed with its optical antipode in a range from >50 % to <100 %. The ee value is calculated as follows:

$$([\text{enantiomer1}] - [\text{enantiomer2}]) / ([\text{enantiomer1}] + [\text{enantiomer2}]) = \text{ee value}$$

The structures shown relate to all possible diastereomers and in terms of a diastereomer to the possible two enantiomers of the compound in question that it encompasses (R or S; D or L).

Experimental examples:

Example 1:

Production of D-cyclohexylglycine

- 100 g (661.5 mmol) D-phenylglycine are dissolved or
5 suspended in 890 ml deionised water, 290 ml isopropanol
and 66.7 ml (802 mmol) 37 % hydrochloric acid. After
addition of 10 g of the Pt/Rh catalyst, 4 % Pt + 1 % Rh on
activated carbon (water content approx. 50 %,
corresponding to approx. 5 wt.% catalyst relative to D-
10 phenylglycine used), the reaction mixture is introduced
into a 2 l hydrogenation autoclave. After being rendered
inert with nitrogen three times, it is rinsed with
hydrogen twice, then a hydrogen overpressure of 8-10 bar
is established and the reaction solution heated to 50-
15 60°C. After approximately 6 to 8 hours, hydrogen uptake is
completed (theoretical amount of H₂ 44.4 l). The
hydrogenator is depressurised and once again rendered
inert with nitrogen three times. The still hot reaction
solution is extracted with a nutsch filter and the
20 catalyst is washed with 200 ml deionised water. The
filtrate is first adjusted at 40-60°C to a pH of 2-2.5
with 50% sodium hydroxide solution, during which process
the first crystals form. It is then stirred for a further
15-30 minutes at this pH and then adjusted to a pH of 5-6
25 with 50% sodium hydroxide solution. The reaction mixture
is cooled in an ice bath to a temperature of 0-10°C, the
product is extracted with a nutsch filter, washed with
300 ml deionised water and dried in a drying oven in vacuo
at 50-70°C.
- 30 The catalyst can be reused several times with no loss of
activity.

Yield: 100-102 g (95.8 - 97.7 %)

^1H -NMR (500 MHz, $\text{D}_2\text{O}/\text{NaOD}$): δ (ppm) = 1-1.26 and 1.53-1.75 (each m, together 11H, cyclohexyl H), 3.02 (d, 1 H, α -H)

In all the cases analysed, the enantiopurity of the D-cyclohexylglycine produced in this way (determined by GC
5 with chiral separation phases) was identical to the enantiopurity of the D-phenylglycine used.

Example 2:

Production of L-cyclohexylalanine

20 g (121 mmol) L-phenylalanine are dissolved or suspended
10 in 200 ml deionised water, 200 ml isopropanol and 12.2 ml (146 mmol) 37 % hydrochloric acid. After addition of 2 g of the Pt/Rh catalyst, 4 % Pt + 1 % Rh on activated carbon (water content approx. 50 %, corresponding to approx. 5 wt.% catalyst relative to L-phenylalanine used), the
15 reaction mixture is introduced into a 1 l hydrogenation autoclave. After being rendered inert with nitrogen three times, it is rinsed with hydrogen twice, then a hydrogen overpressure of 8-10 bar is established and the reaction solution heated to 50-60°C. After approximately 6 to 8
20 hours, hydrogen uptake is completed (theoretical amount of H_2 8.1 l). The hydrogenator is depressurised and once again rendered inert with nitrogen three times. The still hot reaction solution is extracted with a nutsch filter and the catalyst is washed with 50 ml deionised water. The
25 filtrate is first concentrated to low volume in vacuo (the isopropanol largely removed), the residue then adjusted to a pH of 5-6 with 50% sodium hydroxide solution. It is cooled to a temperature of 0-10°C, the product is extracted with a nutsch filter, rinsed with 50 ml
30 deionised water and dried in a drying oven in vacuo at 50-70°C.

Yield: 19.5 g (94.2 %)

¹H-NMR (500 MHz, D₂O/NaOD): δ (ppm) = 0.85-1.0 and 1.1-1.52 and 1.63-1.75 (each m, together 13H, cyclohexyl-H and cyclohexyl-CH₂), 3.3 (t, 1 H, α-H)

5 Example 3:

Production of (2R, 1'RS)-3-(3'-piperidine) alanine x 2 HCl
(2R, 1'RS)-2-amino-(3'-piperidine) propionic acid x 2 HCl)

20 g (120 mmol) 3-(3'-pyridyl)-D-alanine are dissolved in
200 ml deionised water, 200 ml isopropanol and 12.2 ml
10 (146 mmol) 37 % hydrochloric acid. After addition of 2 g
of the Pt/Rh catalyst, 4 % Pt + 1 % Rh on activated carbon
(water content approx. 50 %, corresponding to approx. 5
wt.% catalyst relative to 3-(3'-pyridyl)-D-alanine used),
the reaction mixture is introduced into a 2 l
15 hydrogenation autoclave. After being rendered inert with
nitrogen three times, it is rinsed with hydrogen twice,
then a hydrogen overpressure of 8-10 bar is established
and the reaction solution heated to 50-60°C. After
approximately 4 hours, hydrogen uptake is completed
20 (theoretical amount of H₂ 8.06 l). The hydrogenator is
depressurised and once again rendered inert with nitrogen
three times. The still hot reaction solution is extracted
with a nutsch filter and the catalyst is washed with
deionised water. The filtrate is evaporated in vacuo,
25 12 ml 37 % HCl and 200 ml isopropanol are added, and it is
evaporated again.

Yield: 29 g (98.6 %), according to NMR a mixture of
diastereoisomers (2R, 1'S)- and (2R, 1'R)- 3-(3'-
piperidine) alanine x 2 HCl

Example 4:

Production of L-cyclohexylglycinol x HCl

27.4 g (200 mmol) L-phenylglycinol are dissolved in 220 ml 1 n hydrochloric acid and 200 ml isopropanol. After
5 addition of 3 g of the Pt/Rh catalyst, 4 % Pt + 1 % Rh on activated carbon (water content approx. 50 %, corresponding to approx. 5.5 wt.% catalyst relative to L-phenylglycinol used), the reaction mixture is introduced into a 2 l hydrogenation autoclave. After being rendered
10 inert with nitrogen three times, it is rinsed with hydrogen twice, then a hydrogen overpressure of 8-10 bar is established and the reaction solution heated to 50-60°C. After approximately 6 to 8 hours, hydrogen uptake is completed (theoretical amount of H₂ 13.4 l). The
15 hydrogenator is depressurised and once again rendered inert with nitrogen three times. The still hot reaction solution is extracted with a nutsch filter and the catalyst is washed with deionised water. The filtrate is first largely concentrated to low volume in vacuo and the
20 residue then taken up in 300 ml acetone and 100 ml MtBE added. It is cooled to a temperature of 0-10°C, the product extracted with a nutsch filter, rinsed with MtBE and dried in a drying oven in vacuo at 50°C.

Yield: 34.5 g (96.1 %)

25 ¹H-NMR (500 MHz, DMSO): δ (ppm) = 0.95-1.2 and 1.55-1.75 (each m, together 11 H, cyclohexyl-H), 2.8 (m, 1 H, CH-N), 3.45-3.5 and 3.6-3.65 (each m, together 1 H, CH₂-O), 5.25 (t, 1 H, OH), 7.95 (s, 3H, NH₃⁺).